REMARKS

Entry of the foregoing and reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested in light of the remarks which follow.

As noted in the Office Action Summary, claims 1-20 are currently pending. Claims 11 and 20 stand withdrawn from consideration.

Claim 1 is amended herein to replace the phrase "and/or" for clarification. Basis for the amendment may be found throughout the specification and claims as-filed, especially in claim 1 as-filed.

The specification is amended herein to address an accidental error of omission. Example 1 is amended to recite that the 100 μl competent E. coli cells are mixed with magnetically susceptible particles at 0°C with 500 μg pUC18 dissolved in 30 μl 0.05 M $CaCl_2$. Applicants submit that this is not new matter. For example, the use and benefits of using the magnetically susceptible particles, are discussed at least at page 3, line 27 to page 4, line 10, page 4, line 36 to page 5, line 7, and page 6, lines 13-17, and page 8, lines 2-5. Applicants further note that the step of mixing the particles with, and the effect of the mixture with biological membrane-enveloped structures, is clear in light of the specification as a whole.

Rejections Under 35 U.S.C. §§ 102 and 103

Claims 1 and 7-10 stand rejected under 35 U.S.C. § 102(b), as purportedly anticipated by U.S. Patent No. 5,516,670 ("Kuehnle"). Applicants respectfully traverse. Applicants submit that Kuehnle fails to recite every element of the

presently claimed invention, as amended herein. To anticipate a claim, a single prior art reference must teach each and every element of the claimed invention. *See* M.P.E.P. § 2131; *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987); *Hybritech Inc. v. Monoclonal Antibodies.*

Claims 2, 3, 12 and 16-19 stand rejected under 35 U.S.C. § 103, as purportedly unpatentable over U.S. Patent No. 5,516,670 ("the '670 patent"). The '670 patent purportedly discloses the use of an alternating magnetic field and a field strength of 500 gauss. Applicants respectfully traverse. In order to establish a case of *prima facie* obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation to modify the reference or combine reference teachings, (2) there must be a reasonable expectation of success, and (3) the prior art reference(s) must teach or suggest all of the claim limitations. *See* M.P.E.P. 2142. Applicants respectfully submit that these criteria have not been met in the present Office Action.

Applicants submit that Kuehnle does not recite every element of the claimed invention, as required under 35 U.S.C. § 102, or provide an expectation of success or motivation to modify, as further required under 35 U.S.C. § 103. The path of transport and particle shape are very different from those of the present invention, and the magnetic fields used in Kuehnle cannot be used in the present invention with success. Before turning to Kuehnle in detail, Applicants note that claim 1 is amended herein to remove the use of alternative language with respect to the use of thermal versus kinetic.

The difference in particle shape and transport path

Kuehnle discloses a method for introducing reagents. By way of example, this reference discloses introducing genetic material (*i.e.*, DNA) into biological cells by using magnetizable particles of an acicular shape in solution. The method of Kuehnle uses the steps of forming a monodispersion of the acicular magnetizable particles and contacting the monodispersion with the specimen (a cell or tissue material) at a location close to the focal point of a gradient (non-uniform) magnetic field. The cells and the particles are directly exposed to the gradient magnetic field. The particles align themselves with the direction of the magnetic field and move towards the cells, penetrating the cell membrane and (if necessary) the cell walls. Once the magnetic field is disconnected, the particles stop moving and remain within the cell target. Thus, if the particles are covered with a molecule, such as DNA, the molecule will enter the cell with the particle. The specific acicular shape of the particle in Kuehnle is a requirement in order for the method disclosed to actually function. In fact, the particle must have an acicular shape with a width/length ratio of at least 1:20.

In contrast, the present claims disclose magnetically susceptible particles, which are mixed with biological membrane-enveloped structures, *e.g.* the target cells or cell organelles. The particles recognize and bind to the cells/organelles and are are incubated together to allow for recognition between them. Thus, in the present invention, the magnetically susceptible particles do not require the acceleration or direction given to them with the magnetic field as set forth in Kuehnle to reach the cell surface.

After the particles have located the cell surface target, the cell-particle complexes are exposed to an alternating magnetic field. This field does not in any aspect have an axis of convergence which intersects the specimen and "whose field lines converge to a focal point proximal to the specimen" as required by the Kuehnle reference (*see*, for example claim 1 of Kuehnle).

Kuehnle does not disclose the alternating magnetic field of the present invention; if Kuehnle was altered to arrive at the method of the present invention, its efficacy would be destroyed

An alternating field would not create the effect of aligning and acceleration of the acicular particle as described in Kuehnle. If the method as set forth in Kuehnle utilized an alternating magnetic field, the acicular particles would align with the field direction then flip back and forth in correlation with the frequency of the alternating magnetic field. As a result, they would not achieve the high speed and direction needed to reach and penetrate the target cells. The Kuehnle reference cannot achieve the present invention with an alternating magnetic field. Yet the alternating magnetic field is a required element of the present invention in order to transport of bioparticles into the biological membrane-enveloped structures.

The Office states that as set forth in Kuehnle it is optional to pulse the field. In response, Applicants submit that pulsing of the field is actually a requirement of Kuehnle in order to cover all the cells, or all of the tissue placed in the sample holder. In Kuehnle, the magnetic field is on, then turned off, while the sample holder is moved slightly to expose new cells to the focal point of the magnetic field. These pulses do not have the characteristics of a magnetic field with an alternating field direction.

Further, Applicants submit that there is no expectation of success with Kuehlne. When the alternating magnetic field is applied in the method of the presently claimed invention, the magnetically susceptible particles generate heat due to oscillation of the interior magnetic moment of the particle as well as some heat friction due to minor vibrations and oscillations of the physical body of the particles. The generated heat from the magnetically susceptible particles increase local movements within biological membranes if the particle is attached close to the membrane. The heat further increases the velocity of diffusion of bioparticles in the close vicinity of the magnetic particles. The increased movements within the membranes in combination with an increased rate of diffusion promote the transport of bioparticles and molecules across biological membranes, which in turn facilitate the cellular uptake of said bioparticle or molecule.

In further contrast to Kuehnle, the transport of the magnetic particle itself into the target cell is not always required to transport a bioparticle into the biological membrane-enveloped structure, *e.g.* a cell, using the method as claimed herein. Depending on the diameter of the magnetic particle, different paths are possible. The magnetic particle can itself traverse the membrane, thus acting both as membrane-opener and as a vehicle of transport for a bioparticle attached to its surface. However, if the magnetic particle is too large it will not cross the membrane, but would only provide heat and promote uptake of bioparticles in-between magnetic particle and biological membrane-enveloped structure.

The Office further states that once the particles are in place within its target (*i.e.*, once they have traversed the barrier made up by the cellular membrane) it is possible to manipulate the particles. However, the present invention does not

consider possible actions after the delivery of magnetic particles or molecules into cells or cell organelles. One example of manipulation in Keuhnle, once the particles are in place within its target, is given with the use of an alternating field in the coil 34 (*see* column 7, lines 9-11) which make the particles oscillate within the target. No frequency or field strength is provided, and the particles are already in place such that they are not transporting a macromolecule into a cell across a cellular membrane or organelle membrane. Another example is a manually handled permanent magnet used to rotate the particles within the cells (*see* example 5, column 5, lines 39-45). This manually handled secondary magnetic source is not used in combination with the first magnetic source, which is the converging magnetic field. If the first magnetic source, the converging magnetic field set forth in Kuehnle, is not interrupted, the magnetic particles will continue through the cells until they are stopped at the bottom of the sample holder. Thus, the field is interrupted as soon as the magnetic particles reach their target.

The manually held rod magnet cannot describe two magnetic forces, but can only be one force. Therefore, this rod magnet cannot be defined as two coils exerting an alternating gradient field in-between them with an alternating field direction as described in present invention. Applicants further point out that this magnetic source is held manually in an alternating fashion to rotate the particles. The fact that it has to be held by a human hand limits the frequency of the alternating movement of the manually-held magnet and it is likely difficult to reach frequencies above 1 kHz. A third example of manipulation once the particles are in site is given, where a RF field can be used to heat the particles (depending on the appearance of the particle), is found at column 7, lines 18-24. The use of magnetic particles for

intracellular heating using RF fields, as well as magnetic cell sorting or magnetic separation of molecules, are well known in the scientific and patent literature since the 1970s and is well known both within academia and industry.

In summary, comparing the Kuehnle reference with the presently claimed invention, the path of transport is very different, the particles are fundamentally different in shape, and the magnetic fields used in one are not applicable in the respective other. It would not be possible to interchange the particles or the magnetic fields in between the two methods and still achieve positive results. Thus, not only does Kuehnle fail to recite each element of the presently claimed invention, Kuehnle does not provide motivation to alter the reference to arrive at the present invention or an expectation of success upon doing so.

In light of the above remarks, Applicants request that the rejections under 35 U.S.C. § 102 and § 103 be withdrawn.

CONCLUSION

From the foregoing, further and favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully requested to telephone the undersigned so that prosecution of the application may be expedited.

Respectfully submitted,

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